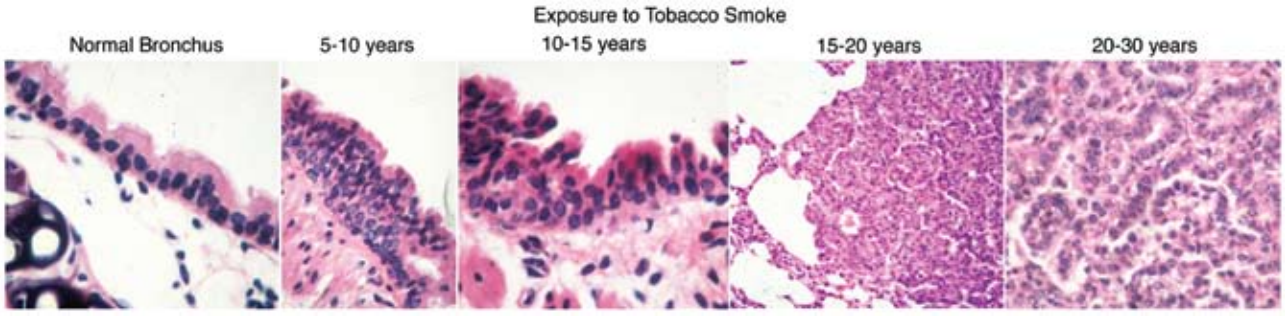
Teaching an Old Drug New Tricks

A drug regularly used to treat diabetes may be effective in preventing lung cancer in smokers.



(Image: J. Weddle)

Exposure to tobacco smoke over a lifetime causes normal cells from a lung bronchus to progress to hyperplasia (5-10 years later), dysplasia (10-15 years later), carcinoma *in situ* (15-20 years later), and, eventually, malignant adenocarcinoma (20-30 years later).

For about 15 years, metformin has been a safe, inexpensive, and widely used treatment for Type 2 diabetes. The drug decreases levels of insulin-like growth factor-1 (IGF-1) and circulating insulin, explaining its role in a disease where the normal insulin response is impaired. Recent research suggests, however, that metformin may also be used as an anticancer drug to prevent lung carcinoma in smokers. IGF-1 is believed to play a crucial role in this form of cancer, and a variety of studies have suggested that, by blocking IGF-1's activity, metformin may inhibit cancer.

Phillip A. Dennis, M.D., Ph.D., Head of the Signal Transduction Section of the Medical Oncology Branch at CCR, and colleagues tested this idea by administering metformin to mice for 13 weeks following exposure to the most prevalent tobacco carcinogen, nicotine-derived nitrosamine (NNK). They found that mice treated with an oral form of metformin showed a reduction in lung tumor burden by about 55 percent compared to untreated mice. This effect was even more profound when the treatment was administered by injection with higher levels of metformin: the drug reduced lung tumor burden by almost 75 percent compared with no treatment. These findings were published in the September 1, 2010 issue of *Cancer Prevention Research*.

The researchers further evaluated the effects of metformin on a series of biomarkers for lung tumorigenesis. They showed a marked inhibition of the cell signaling protein mTOR—which promotes lung tumor growth—related to decreased levels of circulating insulin and IGF-1. "What's interesting is that it didn't appear that lung tissues were responding directly to metformin, but that liver tissues were," said Dr. Dennis. "This showed us metformin works through an unusual mechanism that wouldn't have been discerned if we hadn't used an animal model because an intact liver is needed to respond to metformin and change the circulating levels of IGF-1 and insulin."

Metformin for lung cancer prevention has several advantages, noted Dr. Dennis. "It's oral, it's inexpensive, and it has almost no side effects in nondiabetics." With any chemopreventive agent, minimal toxicity is critical, and metformin was well tolerated in the mice. In fact, the livers of the treated mice not only showed no signs of toxicity, but they actually appeared healthier than those of untreated mice since fewer cases of fatty liver were observed. Although oral dosing is feasible in humans, reaching levels achieved by injection would require development of more potent derivatives of metformin.

This study may be the first to show the potential for metformin to prevent lung cancer. Next, Dr. Dennis' group plans to combine metformin with other preventive agents. "In fact, because metformin and rapamycin work through different mechanisms to inhibit mTOR, we think it might be very interesting to combine those two drugs." The team also plans to test metformin in other model systems and develop a clinical trial to test the drug in people at the highest risk of developing lung cancer.

To learn more about Dr. Dennis' research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?Name=dennis.